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REVIEW ARTICLE

Magnetoencephalography studies in migraine and headache disorders: A systematic review

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Abstract

Background: Understanding the neural mechanisms underlying migraine and other primary headache disorders is critical for the development of long-term cures. Magnetoencephalography (MEG), an imaging modality that measures neuronal currents and cortical excitability with high temporal and superior spatial resolution, has been increasingly used in neurological research. Initial MEG studies showed promise in directly recording cortical spreading depression—a cortical correlate of migraine with aura. However, lately MEG technology has highly evolved with greater potential to reveal underlying pathophysiology of migraine and primary headache disorders, and aid in the identification of biomarkers.

Objective: To systematically review the use of MEG in migraine and other primary headache disorders and summarize findings.

Methods: We conducted a systematic search and selection of MEG studies in migraine and primary headache disorders from inception until June 8, 2023, in Medline, Embase, Cochrane, and Scopus databases. Peer-reviewed English articles reporting the use of MEG for clinical or research purposes in migraine and primary headache disorders were selected.

Results: We found 560 articles and included 38 in this review after screening. Twelve studies investigated resting-state, while others investigated a sensory modality using an evoked or event-related paradigm with a total of 35 cohort and 3 case studies. Thirty-two studies focused exclusively on migraine, while the rest reported other primary headache disorders.

Conclusion: The findings show an evolution of MEG from a 7- to a 306-channel system and analysis evolving from sensor-level evoked responses to more advanced source-level connectivity measures. A relatively few MEG studies portrayed

Abbreviations: AEF, auditory evoked field; CGRP, calcitonin gene–related peptide; CM, chronic migraine; cM1, contralateral primary motor cortex; CMV, contingent magnetic variation; cS1, contralateral primary somatosensory cortex; CSD, cortical spreading depression; DC, direct current; EEG, electroencephalography; EM, episodic migraine; FHM, familial hemiplegic migraine; fMRI, functional magnetic resonance imaging; ISI, interstimulus interval; M1, primary motor cortex; MEF, movement-evoked magnetic field; MEG, magnetoencephalography; MMN, mismatch negativity; NDPH, new daily persistent headache; PAF, peak alpha frequency; S1, primary somatosensory cortex; SS, scintillating scotoma; SSEF, somatosensory evoked field; TTH, tension-type headache; VEF, visual evoked field.

migraine and primary headache disorders as a sensory abnormality, especially of the visual system. We found heterogeneity in the datasets, data reporting standards (due to constantly evolving MEG technology and analysis methods), and patient characteristics. Studies were inadequately powered and there was no evidence of blinding procedures to avoid selection bias in case–control studies, which could have led to false-positive findings. More studies are needed to investigate the affective–cognitive aspects that exacerbate pain and disability in migraine and primary headache disorders.

Plain Language Summary: Magnetoencephalography (MEG) is a brain imaging technique that has been used for more than three decades to study changes in the way the brain works during migraine and headache, but we still have more to learn about what value this type of imaging can bring to clinicians and patients. In this study, we reviewed all relevant studies to date that used MEG, and we learned that many of the studies we reviewed did not have adequate control measures or statistical power to make firm conclusions, and many also portrayed migraine and headache as sensory processing disorder. Carefully designed research using MEG is needed because this technique can help us identify brain mechanisms related to emotion and cognition, which could ultimately help us understand more about why migraine tends to be such a disabling condition.

KEYWORDS
electrophysiology, headache, magnetoencephalography, migraine, neuroimaging, neurophysiology

INTRODUCTION

Migraine and other primary headache disorders represent one of the most disabling forms of pain. There is a growing interest in understanding the underlying neurobiology of migraine using imaging modalities. Magnetoencephalography (MEG)[1] is a non-invasive neuroimaging modality with direct access to the electrophysiological activity of the entire brain. Though MEG appears to be equivalent to electroencephalography (EEG) in terms of millisecond temporal resolution and spectral differentiation ability, MEG can locate the origin of underlying sources with superior spatial resolve compared to EEG.

According to neurogenic theory, migraine is considered a neuronal dysfunction characterized by cortical spreading depolarization or depression (CSD) that leads to hyperexcitability of cerebral cortex and vascular changes.[2] The neurogenic theory gained popularity when CSD[3] originating from the visual cortex was found to be a physiological correlate of migraine aura (visual disturbances that accompany headache) by initial breakthrough studies.[4] While EEG was silent to the CSD phenomenon,[5] early MEG studies showed promise in localizing CSD activity in the brain.[6,7]

Ever since these initial promising findings from the early 1990s, many studies have investigated the phenomena of cortical hyperexcitability in migraine and other primary headache disorders using MEG. However, studies have been heterogeneous in their designs, as well as population demographics and phenotypes. In addition, MEG infrastructure has also evolved from a few induction coil magnetometer sensors from the 1990s to more sophisticated multichannel superconducting quantum interference devices[8] comprising hundreds of sensors, with next-generation wearable optically pumped magnetometers[9] on the horizon. As a result, analysis techniques have evolved, making it possible to study deeper subcortical structures in addition to cortical sources. On the other hand, these advances have also contributed to additional heterogeneity in study design, data collection, analysis, and interpretation.

The goal of this systematic review was to describe the use of MEG in investigating migraine and other primary headache disorders, and to summarize MEG findings published since the inception of MEG. Attention was given to resting-state and event-related studies that investigated specific sensory modality to correlate MEG findings with clinical parameters of migraine that are hallmarks of disease manifestation and disability.

METHODS

This systematic review was not subject to institutional review board approval. It was conducted following Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and

pre-registered using Open Science Registries (protocol link https://osf.io/7ujkz). The full dataset, statistical code, and data collection form have been deposited in the Open Science Framework at https://osf.io/8wvsa/?view_only=3a5ce45ef822411a9f82141a9658f3dc.

Search strategy

A comprehensive search strategy was developed with a medical librarian (N.N.) to identify potentially relevant articles including the use of MEG to investigate or understand primary headache disorders. Indexing terms and keywords with truncation were combined using Boolean and proximity operators. No limits were imposed on the search. Full search syntax can be found in the supporting information. Because the initial goal of this paper was to describe the use of MEG in migraine and other primary headache disorders to date, we did not include gray literature (non-traditional/non–peer reviewed) or contact authors.

The following databases were searched from inception until June 8, 2023: Medline (Ovid), Embase (Ovid), Cochrane Library, and Scopus. A search validation was run comparing three Medline records with the results of the search. The search strategy picked up all three records.

Inclusion/exclusion criteria

For inclusion, articles were required to be peer reviewed and written in English; must have acquired MEG for clinical and/or research purposes (regardless of whether a clinical outcome measure was reported); utilized experimental, cohort, case–control, cross-sectional, case series, or case report design; included study participants of any age with chronic migraine (CM), episodic migraine (EM), cluster headache, tension-type headache (TTH), medication-overuse headache, or other types of headache not mentioned in exclusion criteria; and included healthy controls only when comparing to a headache population.

Articles with the following characteristics were excluded: abstract only; meta-analysis, systematic or narrative review, clinical guidelines, commentaries, trial protocols; studies not utilizing MEG; patient population wherein headache disorder was reported as a comorbidity (e.g., stroke, epilepsy); studies on facial pain, neuralgia, and other chronic pain disorder populations.

Screening

Covidence software was used to manage, screen, deduplicate, and document this systematic review. Titles and abstracts were screened independently for inclusion criteria by two authors (R.G., E.D.) with a third to settle disagreements by majority vote (O.H.). Full texts were then screened independently for inclusion/exclusion criteria by two authors (R.G., E.D.). R.G., E.D., and O.H. discussed all disagreements at the full text screening stage to reach consensus. Risk of bias evaluation was not carried out due to the aims of this review and the primarily non-interventional design of most included studies.

Data extraction

Using a REDCap structured data collection form, all data were extracted twice independently by two members of the study team (N.S.M., E.D.), and then screened for disagreements (O.H.). Disagreements were settled via study team discussion (N.S.M., E.D., R.G.) and documented as to whether they were data entry errors, extractor oversight, or due to confusing information from the article in question.

The following information was collected from each article: title; publication year; patient population; the number of participants for each diagnosis type; the number of healthy controls using either the same protocol or a different protocol (where applicable); patient characteristics including presence or absence of aura, age, and sex; country and institution of authors; MEG characteristics including type of MEG, number of channels, time points of MEG collection; task or paradigm information; MEG analysis information; study design information; and whether the study included clinical outcome information.

Our original goal for this review was to summarize the use of MEG to date to study migraine, without particular attention to the findings of each study (i.e., a strictly methodological review). This was due to the expected high variability in MEG methods, research questions investigated through MEG, and subsequent interpretation. However, fewer studies were returned than anticipated, and the choice was made post hoc by the study team to narratively present findings, in addition to the systematic presentation of MEG methodology. Thus, the main findings of each study were not extracted as part of the data collection form but were verbally discussed among the study team involved in extraction (R.G., N.S.M., E.D.) to arrive at a consensus.

Data summarization

Descriptive tables were prepared (N.M.) using SAS Studio version 3.81 to summarize study characteristics using counts with proportions, means with standard deviations, or medians with full ranges or interquartile ranges, as appropriate based on data type (see Table S1 in supporting information). Because of the nature of the review, missing data are meaningful and included in the tables as counts of articles that did not include the data item in question. MEG findings are presented qualitatively. This is a descriptive study without statistical inference.

RESULTS

Our search results identified a total of 560 studies initially and 38 studies[6,7,10–45] ultimately were included in this review. The detailed

screening flowchart is presented in Figure 1. Most of the identified studies were published between 2010 and 2019 and originated in the United States, Taiwan, and China (Figure 2).

Clinical and demographic summary

Of included studies, 14 primarily studied persons with EM only[11,14,16,19,20,26–28,32,33,38,39,41,44] (i.e., monthly attacks <15), 1 studied persons with CM only[43] (i.e., monthly attacks >15), 9 studied[13,15,18,25,34–36,40,45] both persons with EM and CM, and 8 studies[6,7,10,21,22,29,37,42] did not explicitly state if the persons had EM or CM. There were also other single studies with a primary focus on familial hemiplegic migraine (FHM),[23] cluster headache,[31] scintillating scotoma[24] without subsequent migraine headache, new daily persistent headache,[30] TTH,[17] and persistent visual aura.[12] Overall, there was 1 observational case study,[24] 33 observational case–control studies,[6,7,11,12,14–22,25–30,32–45] 2 interventional case studies,[23,31] and 2 interventional cohort studies.[10,13]

Sixteen studies[6,10–12,19,21,22,25,28,32,33,35,38–40,42] involved participants with and without aura, 11 studies[14–18,20,26,27,37,41,44] included subjects only without aura, 3 studies[7,23,24] included subjects only with aura, and 8 studies[13,29–31,34,36,43,45] did not explicitly state the presence or absence of aura.

Twenty-nine studies[6,7,10–22,25–33,41–45] were of an adult population defined as ≥18 years of age, 7 studies[23,34,36–40] were

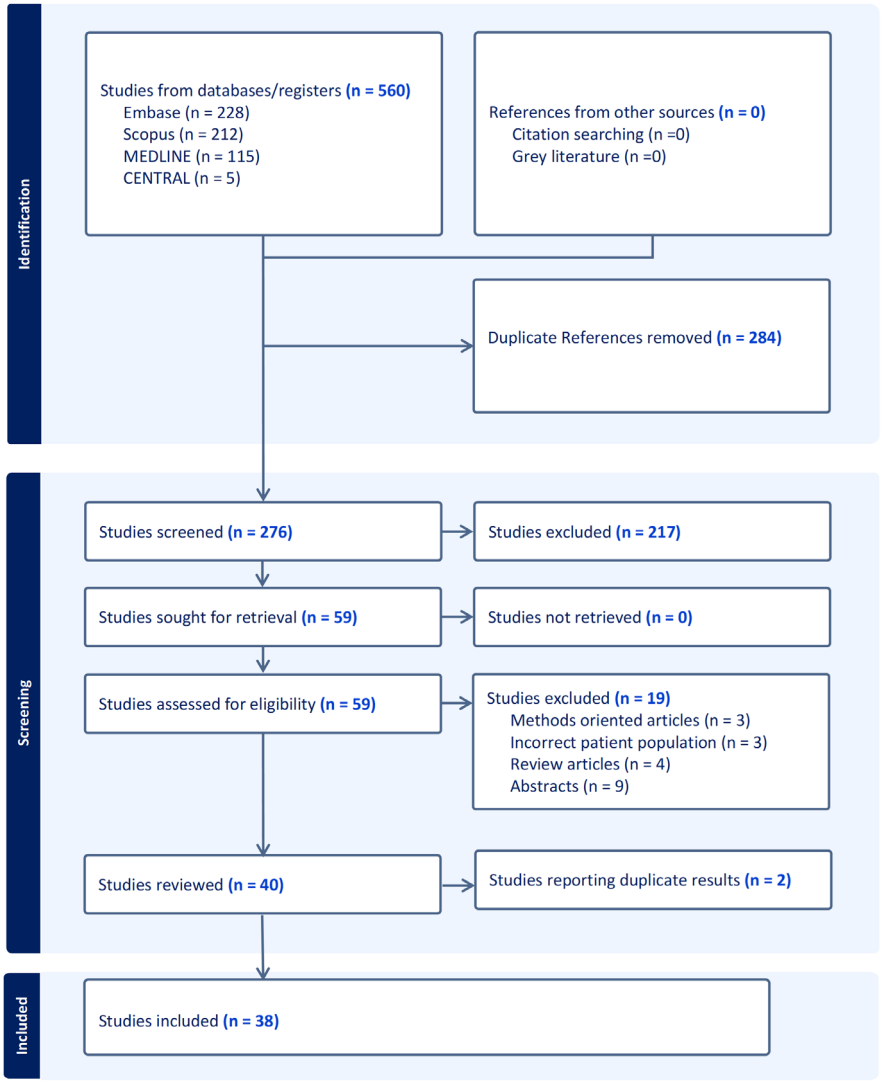

FIGURE 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart of literature selection. The flowchart shows our literature search and the number of studies excluded at different stages of the literature search procedure. Examples for exclusion reasons at screening stage include false and unrelated topics. Examples of exclusion reasons while assessing for eligibility include magnetoencephalography methods-oriented articles; articles pertaining to related disorders such as facial pain, trigeminal neuralgia, and so on; conference proceedings or abstracts; and review articles. After reviewing all studies, two historic articles[46,47] were excluded because they reported the same results from the same cohort, though the articles were not completely identical. [Colour figure can be viewed at wileyonlinelibrary.com]

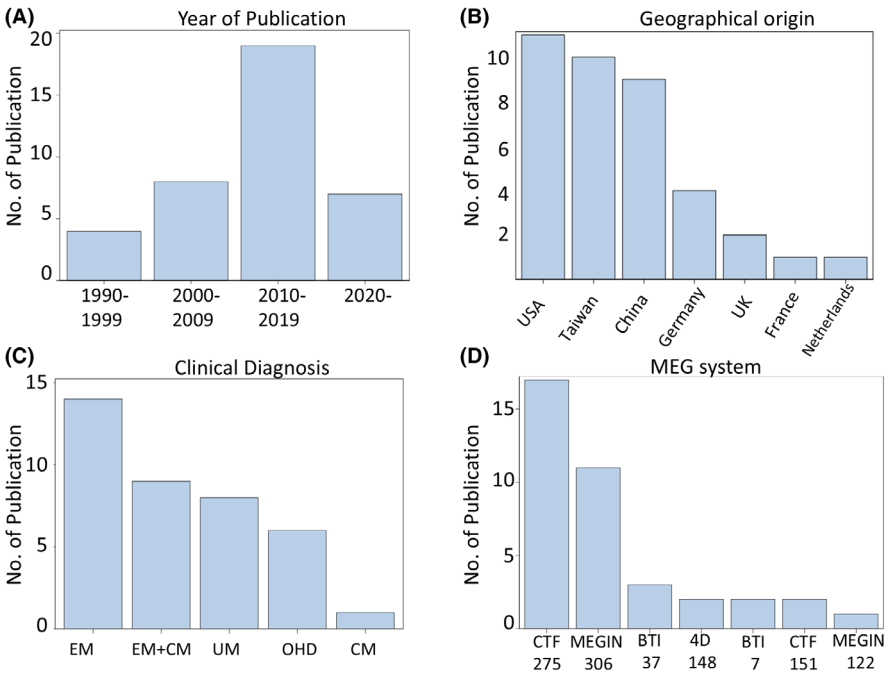

FIGURE 2 A, Total number of search results per decade for the articles reviewed in this article. B, Geographical location of primary institute where research was conducted. C, Summary of clinical diagnosis. D, Summary of MEG systems used in migraine and OHD (manufacturer and number of channels specified. MEGIN previously called Elekta Neuromag). CM, chronic migraine; EM, episodic migraine; MEG, magnetoencephalography; OHD, other headache disorders; UM, unspecified migraine. [Colour figure can be viewed at wileyonlinelibrary.com]

performed on adolescents (ages 13–17), and 1 study[35] was performed on children under the age of 13. One case study[24] did not report the age.

Thirty studies[6,7,10–15,17,18,20–22,25–27,29,30,32,34,35,37–45] included participants from both sexes, five studies[16,19,28,33,36] were exclusively of female sex. Two case studies[23,31] enrolled one male participant and one case study[24] did not report the sex of the participant.

Three case studies[23,24,31] and two interventional cohort studies[10,13] did not include a control cohort. All other studies included a healthy individual and/or another population without the headache disorder under investigation as a control.

Eighteen studies[7,10,11,13,14,16,18–20,25–27,29,32,41,42,44,45] took place during the interictal interval only, which was inconsistently defined (e.g., within ± 3 days of an attack). Eleven studies[6,12,15,17,21–23,33,37,39,40] collected data at least partially or completely during ictal states. Seven studies[24,28,30,33–36] collected data during ictal periods. Two studies[31,43] did not explicitly state the time of MEG data collection.

Preventative, acute, and non–migraine-related medication were controlled and documented to varying degrees, though four studies[6,22,24,30] did not explicitly state medications relative to MEG scan.

MEG and study design–related summary

Nineteen studies were performed in a CTF machine[16,20,24,27–29,31–41,44,45] (17 used a 275-channel, while 2 used a 151-channel machine). Twelve studies[11–15,17,18,23,25,26,30,43] used a MEGIN system (previously called Elekta/Neuromag) with 11 studies using a 306-channel system and 1 study using a 122-channel system. Two studies[7,10] used a 148 channel 4D-neuroimaging system, while five older studies[6,19,21,22,42] used a 7- or 37-channel BTI system.

Thirteen studies[16,27,30,33–40,42,45] included both sensor- and source-based analysis. Four studies[6,22,23,32] were only based on sensor-level data, while 21 studies[7,10–15,17–21,24–26,28,29,31,41,43,44] only performed source-level analysis. Analysis included investigating amplitude, latency, and/or oscillatory power related to event-related fields in the sensor level, or source strength and location in relation to event-related fields or resting-state. Six studies[20,25,26,29,32,44] performed some type of connectivity analysis at either the source or sensor level.

Of the studies that reported data based on source analysis, 9 studies[7,11–15,19,21,42] used an equivalent current dipole (ECD) method, 13 studies[20,24,28,29,31,33,34,36–38,44,45] used linearly constrained minimum variance (LCMV) or another type of beamformer, 8 studies[17,18,25,26,30,40,41,43] used a distributed source imaging technique such as minimum norm estimate (MNE), and 4 studies[10,16,27,39] used another type of source imaging technique.

Modality-based methodological and narrative summary

Out of 38 studies, 12 were resting-state studies, while the other 26 were event-related task-based studies. The 26 event-related studies

were further classified based on the modality investigated as (1) visual,[7,10–16] (2) auditory,[40–42] (3) somatosensory,[17–21] (4) motor,[33–39] and (5) affective/emotion-based studies.[43–45] Figure 3 summarizes the cortical areas identified by various modality-based MEG studies. Tables S2–S6 in supporting information summarize the selected articles based on the modality.

Visual modality

Eight studies used a visual stimulation paradigm to investigate the excitability of the visual cortex. Two of those studies used a circular checkerboard,[7,10] while others[11–16] used a rectangular checkerboard stimulating the left hemifield with varying frequency and check sizes (though 120′ was found to be the most optimal[14] and used by majority of studies). Six studies[11–16] investigated the progression of 100 ms visual evoked field (VEF; commonly referred to as P100m) resulting from stimulus repetition, while two studies[7,10] investigated direct current (DC)–low-frequency shifts in the MEG signals. All eight studies examined adults with migraine during the interictal or ictal period. One study[12] also examined persons with persistent visual aura compared to persons with migraine and healthy controls.

Narrative summary of findings

The studies that investigated P100m unanimously reported alteration in the VEFs in the headache population compared to a control population. Repetitive stimulus presentation significantly increased the P100m response amplitude in the headache population indicating potentiation,[12–15] while the control population showed a decrease indicating habituation or no change. Within the headache population, CM (with persistent cephalic pain) and ictal cohorts seemed to show the greatest increase in P100m magnitude,[15] followed by the interictal group.[14] Compared to any migraine population, persons with persistent aura were found to have the greatest increase in P100m amplitude with stimulus repetition indicating sustained hyper-excitable state of the visual cortex.[12] Interestingly, one study[14] reported that in the peri-ictal period, the P100m response returned to normality compared to interictal period. Supporting the view that increased P100m could be a potential biomarker of chronic headache disorder, persons that remitted from CM to EM after topiramate treatment showed a decreased P100m amplitude.[13] In relation to the latency of the P100m component, one study[16] reported a prolongation, while another reported shortening especially in migraine with aura cohort.[11] The source location of the P100m was reported to be in the primary visual (striate) cortex by all studies. Only one study[16] investigated the spectral oscillatory power

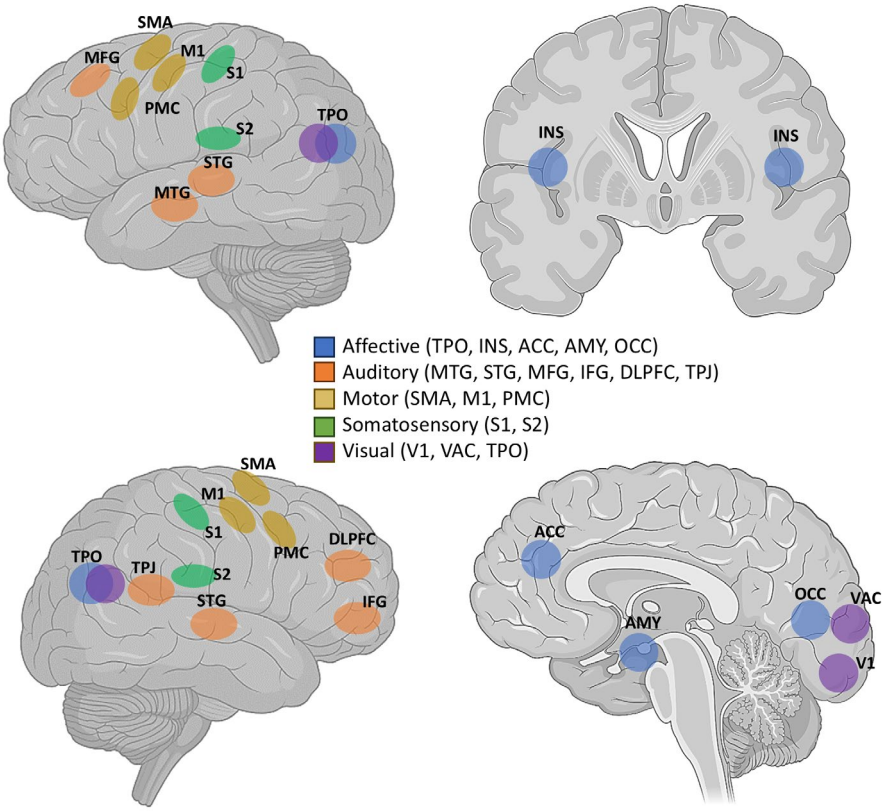

FIGURE 3 Brain areas involved in different modalities investigated in migraine and other primary headache disorders. Brain templates adapted from BioRender.com. ACC, anterior cingulate cortex; AMY, amygdala; DLPFC, dorsolateral pre-frontal cortex; IFG, inferior frontal gyrus; INS, insular cortex; M1, primary motor cortex; MFG, middle frontal gyrus; MTG, middle temporal gyrus; OCC, occipital cortex; PMC, pre-motor cortex; S1, primary somatosensory cortex; S2, secondary somatosensory cortex; SMA, supplementary motor area; STG, superior temporal gyrus; TPO, temporal–parieto–occipital junction; V1, primary visual cortex; VAC, visual association cortex. [Colour figure can be viewed at wileyonlinelibrary.com]

in relation to the visually evoked fields, with the primary finding that cortical spectral power in the 100–1000 Hz range and source strength in the 5–1000 Hz range were decreased in the acute migraine without aura group compared to healthy controls. The same study reported that neural responses in the 5–300 Hz range were observed beyond the visual cortex, especially in the parietal and temporal regions.

The studies[7,10] that investigated DC–low-frequency shifts in the MEG signals used the visual stimulation paradigm to excite the visual cortex, rather than to investigate the evoked fields. Overall, DC shifts representing CSD were observed in the ictal migraine with aura cohort, but not in healthy controls.[7] Further, prophylactic treatment with sodium valproate reduced the incidence of DC shifts and attacks, indicating DC shifts could be potential markers of chronic headache.[10] Like P100m responses, DC shifts were localized to the primary visual cortex and extended locations including parietal and temporal areas.

Neither the visual P100m amplitude/latency nor the DC shifts correlated with any clinical outcome parameters. However, in persons with persistent visual aura, P100m amplitude change correlated negatively with illness duration supporting the non-progressive nature of cortical excitability.[12] In summary, the MEG studies that investigated visual modality reported increased excitability of the visual cortex in persons with migraine, which subsided after select prophylactic treatments.

Auditory modality

Three studies investigated the excitability of the auditory cortex using different auditory stimulation paradigms. Two studies[41,42] investigated contingent magnetic variation (CMV) which is a surrogate marker of attention evoked by conditioning stimuli in anticipation of a forthcoming target stimuli, while one study[40] investigated mismatch negativity (MMN), which is a marker of attention to target stimuli that is deviant from standard targets; that is, oddball response. Two studies[41,42] investigated adults with migraine, while one studied adolescent cohort during ictal periods.[40]

Narrative summary of findings

The 100 ms auditory evoked field (AEF), commonly referred to as M100, was not found to be significantly different in persons with migraine compared to healthy controls.[40,42] However, the amplitude of the M150 component was found to be reduced in adolescents with migraine during ictal periods, suggesting increased inhibition.[40] Ictal migraine also showed decreased MMN amplitude and delayed MMN latency, suggesting sensory–memory and discrimination abnormalities.[40] While the M100 and M150 responses were localized to the primary auditory cortex, the MMN was localized to the bilateral superior temporal, right inferior frontal gyrus, and left middle frontal gyrus.

The CMV exhibited a higher amplitude in persons with migraine compared to healthy controls, suggesting elevated orienting "bottom-up" response. This was further supported by greater evoked response to distracting sounds (orienting component of the N1 and re-orienting negativity) and target sounds (orienting component of the N1). Further, individuals with migraine also exhibited enhanced processing of informative trials, indicating enhanced top-down recruitment.[41] While the bottom-up responses were localized to the left superior and middle temporal, right temporal–parietal junction, and the right dorsolateral prefrontal cortex, the top-down responses were localized to right operculum and temporal–parietal junction.[41]

None of the studies reported any correlation between the AEFs and clinical outcome parameters. In summary, the MEG studies investigating auditory modality report (1) increased cortical inhibition and decreased oddball discrimination anomalies during ictal periods and (2) enhanced bottom-up and top-down attentional processes during interictal periods.

Somatosensory modality

Five studies investigated the excitability of the sensorimotor cortex using different somatosensory stimulation paradigms. The excitability of the primary somatosensory cortex (S1) was investigated using either an electrical stimulation (delivered to the median nerve[19,20] or paired pulse delivered to the index finger[17,18]) or a pneumatic (mechanical) stimulation delivered to the lips and fingers.[21] All studies examined adults with migraine. One study[17] also examined persons with TTH compared to persons with migraine and healthy controls. Four studies[17–20] were performed during the interictal period, while one study[21] included both ictal and inter-ictal periods.

Narrative summary of findings

One study[19] that used median nerve stimulation with different interstimulus intervals (ISIs) investigated the 20 and 35 ms somatosensory evoked fields (SSEFs) on the contralateral S1 (cS1), commonly referred to as N20m and P35m. Compared to healthy controls, persons with migraine were found to exhibit an increased amplitude of N20m at both sensor and source level at all ISIs, which also positively correlated with attack frequency. Another study[20] that used median nerve stimulation to excite the cS1 investigated the functional connectivity between cS1 and other brain regions. Compared to healthy controls, persons with migraine were found to exhibit increased connectivity between S1 and prefrontal areas that were frequency specific and correlated with headache frequency.

Two studies[17,18] that used a paired pulse paradigm measured the cS1 excitability in terms of sensory gating, a phenomenon in which the evoked response to repeated stimuli is reduced due to cortical inhibition. The gating ratio—that is, ratio of second response to first response—was found to be increased in both persons with CM[18] and TTH[17] compared to healthy controls, but not in persons with EM. cS1 gating ratio was positively correlated with headache frequency in persons with migraine,[18] but not in those with TTH.[17]

The study[21] that used a pneumatic stimulator to investigate the evoked response between 25 and 60 ms post-stimulation found no difference between controls and persons with migraine. In summary, MEG studies investigating somatosensory modality using electrical

stimulation in a migraine population reveal (1) increased cortical excitability and connectivity correlated with headache frequency and (2) increased cortical disinhibition in persons with migraine and TTH, with correlation to headache frequency observed in persons with migraine.

Motor studies

Seven studies[33–39] investigated the excitability of the primary motor cortex (M1) using an auditory cued brisk finger tapping paradigm. All studies examined a pediatric population with acute migraine, except one that studied adult female population.[33] Studies varied by whether the data were collected during ictal or interictal periods.

Narrative summary of findings

All studies investigated movement-evoked magnetic fields (MEFs), commonly referred to as MEF1 and MEF2, which occur around 50 and 100 ms of movement onset, respectively. The MEF latency was found to be delayed or prolonged in participants with migraine during ictal periods[33–38] compared to healthy controls, but not during interictal periods.[37,38] Further, persons with CM were found to exhibit higher latency and stronger MEFs beyond 150 ms compared to acute EM when experiencing an attack.[35] In addition, increased amplitude of MEFs was observed in ictal cohorts, compared to interictal cohorts[37] and healthy controls.[36,37]

While the MEFs were characterized at a sensor level (over the contralateral M1 [cM1]), all studies also investigated the spectral power during finger movement at a source level. Compared to healthy controls, people with migraine were found to exhibit increased gamma and high gamma power during ictal periods, while exhibiting a decreased power during interictal periods.[37,38] The power changes were predominantly localized to cM1 in healthy cohorts, while people with migraine showed additional activation in the supplementary motor areas,[33–38] ipsilesional sensorimotor cortex,[33,35,38] visual cortex,[35,38] and deep brain areas[35] (in persons with CM). Neither the MEF parameters nor the spectral power were found to be correlated with clinical outcomes.

One study[39] investigated spatial heterogeneity of cortical excitability across both auditory and motor domains. Heterogeneity was defined as the difference between the auditory activation and motor activation both within and across hemispheres. Individuals with migraine were found to exhibit greater heterogeneity at higher gamma frequency bands that correlated with headache frequency.[39] In summary, MEG studies investigating the motor system in people with migraine reveal (1) increased cortical excitability of the sensorimotor cortex indicated by enhanced MEFs, power changes in high gamma bands, and heterogeneity, and (2) cortical dysfunction indicated by delayed MEF latency.

Affective studies

Three studies[43–45] investigated cortical excitability and activation while evoking negative emotion using human faces[44,45] or fear using painful stimuli.[43] All studies examined adults with migraine during the interictal period, though one study[43] did not explicitly state the time period of data collection.

Narrative summary of findings

Investigation[45] of the evoked response to faces that conveyed negative emotion found that amplitude of 100 and 200 ms responses, referred to as M1 and M2, were lower in persons with CM compared to healthy controls. Further, spectral power between 30 and 100 Hz during M1 and M2 was found to be lower in both CM and EM, and this negatively correlated with index of depression and attack frequency. Though the sources of M1 and M2 were found to be in the occipital and parietal–temporal–occipital cortex, respectively, in all groups, people with migraine showed additional activation in the amygdala and anterior cingulate cortex compared to healthy controls who showed activation in the prefrontal cortex. Another study[44] that investigated the effective connectivity between brain regions in response to emotional faces found greater connectivity across multiple frequency bands (specifically gamma) between prefrontal cortex and temporal lobe in people with acute migraine. The connectivity was also found to be negatively correlated with history, attack frequency, duration, and index of depression and anxiety. Pain-related fear investigated using a fear-conditioning paradigm[43] in persons with CM, compared to fibromyalgia and healthy controls, showed activation of the bilateral amygdala and insula in all three groups. However, habituation to fear was noted in persons with CM and healthy controls, leading to speculation that aberrant amygdala response is not a brain signature of CM. In summary, MEG studies investigating affective response in people with migraine, either through negative emotion or fear reveal (1) activation of brain regions such as the amygdala (fear), insula (salience), and anterior cingulate (affect) and (2) increased cortical broadband connectivity.

Resting–state studies

Twelve studies[6,22–32] investigated cortical excitability during resting-state using source-level spectral activity or power,[23,24,26–28,30,31] source-level functional connectivity,[25,26,29,30,32] or sensor-level modulations.[6,22] Eight studies[6,22,25–29,32] investigated adult persons with migraine, while one study investigated persons with new daily persistent headache[30] (NDPH). Three other studies were case reports on FHM[23], cluster headache,[31] and scintillating scotomas[24] (SSs). Studies varied by whether the data were collected during ictal or interictal periods. Figure 4 summarizes the cortical areas identified by various resting-state MEG studies. Table S7 in supporting information summarizes all the selected resting-state articles.

Narrative summary of findings

During resting-state people with migraine were found to exhibit increased power in the gamma[27,28] frequency band, compared to

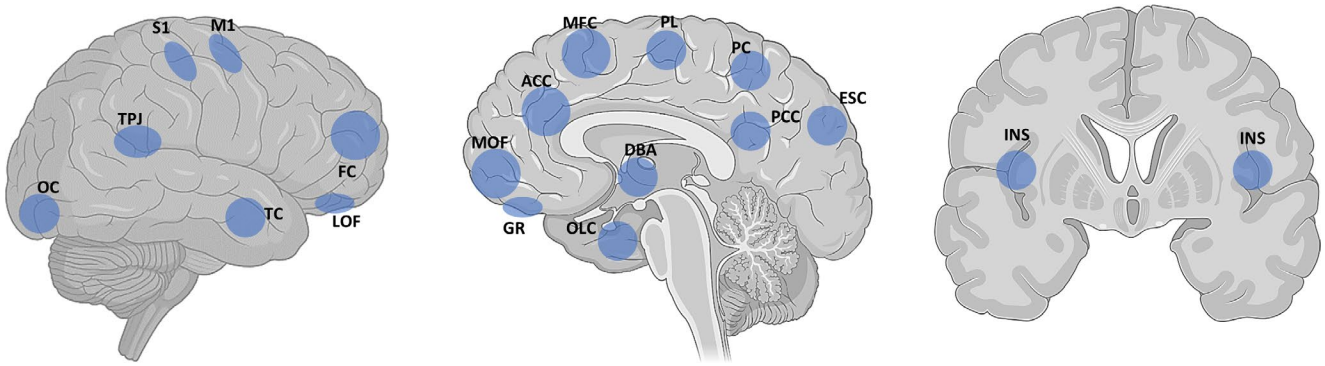

FIGURE 4 Brain areas involved during resting-state investigated in migraine and other primary headache disorders. Brain templates adapted from BioRender.com. ACC, anterior cingulate cortex; DBA, deep brain areas; ESC, extrastriate cortex; FC, frontal cortex; GR, gyrus rectus; INS, insular cortex; LOF, lateral orbital frontal; M1, primary motor cortex; MFC, medial frontal cortex; MOF, medial orbital frontal cortex; OC, occipital cortex; OLC, olfactory cortex; PC, precuneus; PCC, posterior cingulate cortex; PL, paracentral lobule; S1, primary somatosensory cortex; TC, temporal cortex; TPJ, temporal–parietal junction. [Colour figure can be viewed at wileyonlinelibrary.com]

healthy controls. Spatially, the increase was noted in the frontal,[27,28] temporal-occipital,[27] and deep brain areas,[28] with gamma power in the frontal areas negatively correlating with history of migraine.[28] Though the gamma power increases were pathological, unlike in healthy controls, it was not found to correlate with pain sensitivity in people with migraine[26] indicating cortical dysfunction. Persons with NDPH during ictal periods showed increased power in theta, alpha, gamma, and ripple (80–200 Hz) frequency bands, predominantly localized to the frontal and temporal regions.[30] A case study[23] on one participant with FHM also reported increased delta activity on the temporal regions. Suppression of alpha-beta band (desynchronization) over the occipital regions was observed in FHM[23] and during auras in a participant with SS.[24]

A study[32] that investigated global functional connectivity in people with migraine found increased functional connectivity in the delta band localized to the frontal area and the theta band localized to the occipital area in individuals with aura. Another study[25] that looked at the functional connectivity in the pain networks reported a decreased connectivity in the beta bands localized to S1, bilateral anterior cingulate, in both EM and CM.

The studies[6,22] that looked at sensor-level modulations of spontaneous resting-state activity in people with migraine reported observing (1) large amplitude waveform, (2) long duration decrements, (3) long duration large amplitude changes in DC (0–50 Hz) and/or alternating current (0.1–50 Hz) frequency ranges over temporal–parietal–occipital junction, which were absent in healthy controls.

In summary, MEG studies investigating resting-state power and connectivity in people with migraine reveal (1) increased power in the gamma band localized to frontal and temporal regions, (2) increased functional connectivity in delta and theta bands localized to frontal and occipital, (3) decreased connectivity in the beta band localized to pain networks, and (4) abnormal modulation in spontaneous resting-state activity in temporal–parietal–occipital areas.

DISCUSSION

We have identified and summarized 38 original research articles published from inception of MEG until June 2023 that employed heterogeneous approaches to investigate different aspects of migraine (32 studies) and other primary headache disorders (6 studies). To our knowledge, this is the first systematic review of MEG studies in migraine and primary headache disorders. There have been four previous non-systematic reviews including MEG studies. The most recent article,[48] by Chen et al., reviewed brain excitability from both EEG and MEG literature in TTH. Another article[49] by the same group reviewed MEG studies on visual cortex excitability in CM pathophysiology. The other two review articles[50,51] were more than 20 years old when MEG technology development was in its nascent stages. Both these articles supported the role of MEG in detecting CSD in persons with migraine with aura. In this review, we employed a wider search strategy to capture all research articles employing MEG including cross-sectional, longitudinal, and descriptive studies to study migraine and other primary headache disorders for a broader overview. We then categorized the articles based on whether they were event-related or spontaneous resting-state studies. Event-related studies were further categorized based on the specific modality investigated, namely visual, auditory, somatosensory, motor, and affect. The event-related studies investigated cortical evoked fields and/or cortical rhythms (oscillatory power) in various frequency bands. A relatively few articles reported connectivity of different brain areas in the resting-state or in a hyperexcitable state.

Suitability of MEG for migraine

Overall, the gathered evidence supports the understanding of migraine as an alteration of cortical excitability and functional connectivity from a normal state. The alterations differentiating the patient population from healthy controls were observed not

only during ictal periods but also in the interictal periods. MEG is a well-suited modality to investigate migraine pathophysiology given its high temporal and superior spatial resolution. It is specifically suitable for studying large-scale brain dynamics with whole-brain coverage. Further, MEG is silent (unlike functional magnetic resonance imaging [fMRI]) and non-invasive, with low sensitivity to uncertainties about tissue conductivities, and direct measurement of underlying neural activity independent of neurovascular coupling. The latter aspect of MEG was critical in revealing the neuronal processes underlying visual aura, referred to as the CSD,[2] that often accompany the migraine. The number of interictal MEG studies outweigh the number of ictal studies, which could be partly attributed to the difficulty in getting the participants to the scanner during attacks.

Migraine portrayed as a sensorimotor disorder

The results of the event-related studies support the idea that migraine is primarily a sensory disorder with altered processing of sensory stimuli, especially of the visual system. The number of visual studies outnumbered other modalities, given visual disturbances instigate and sustain migraine more than other modalities. A consistent finding among visual studies was the potentiation effect—that is, increased P100m amplitude in response to stimulus repetition, even in those without aura, compared to healthy controls. Further corroborating the P100m were the presence of low-frequency shifts signifying CSD. Importantly, these measures were modified after prophylactic treatment or remission, though there was no linear correlation with any clinical outcome measures. Along a similar vein, sensorimotor cortical excitability was pronounced in people with migraine with both SSEFs and MEFs showing increased amplitude and increased disinhibition to repeated stimuli. On the contrary, the auditory cortical excitability in terms of AEFs were not found to be different, though there was evidence of impaired information processing, discrimination, and attentional responses in people with migraine.

Studies on affect are lacking

Fear avoidance and disability have occupied a central role in migraine and primary headache disorders for decades.[52] Yet, MEG studies have predominantly focused on the sensory–discriminatory component. Our search only yielded three studies that examined affective dimension using an emotion- or fear-based paradigm. Emotional disturbances were noticed in terms of altered cortical excitability and connectivity between brain regions that correlated with affective dimension. Fear of pain, on the other hand, localized to the amygdala, was not found to be aberrant in persons with CM compared to fibromyalgia, which shares similar features to CM.[43] This lone study that used a classical conditioning task seems to be at odds with literature that reports fear of pain and subsequent avoidance behavior exert substantial influence on persons with headache. Further studies with different designs are needed to investigate fear conditioning and avoidance in migraine and primary headache disorders.

Hyperexcitability versus dys-excitability

While the terminology "hyperexcitability" is widely used in both headache and epilepsy literature,[53] the term "dys-excitability" is used to exclusively characterize the interictal migraineous brain.[54] Dys-excitability refers to sequential hyper- and hypo-excitable states resulting from CSD that precede migraine attacks. In fact, many studies have suggested "dys-excitability" to better characterize pathophysiological events associated with headache attacks.[55,56] Dys-excitability is also implicated with decreased habituation/increased potentiation and hypervigilance to external sensory stimuli in anticipation of pain.[57] Future MEG studies in migraine and headache disorders should address and investigate pathophysiology of cortical dys-excitability, and its implication for psychopathological symptoms that accompany headache.

Resting-state studies are heterogeneous

Unlike event-related studies, resting-state MEG studies are appealing because they are easy to conduct and could lead to identification of potential objective biomarkers for migraine and primary headache disorders. However, our findings from MEG studies are mixed. Persons with chronic pain, in resting-state, frequently exhibit lower peak alpha frequency (PAF), slowing of alpha peak, higher gamma power, and higher theta power/connectivity.[58] While lower PAF or PAF slowing was not evident in a migraine or headache population, suppression of alpha specifically over occipital regions was observed during visual aura and ictal periods. When considering gamma power and theta connectivity, persons with migraine seem to share commonalities with chronic pain. The findings are compatible with thalamocortical dysrhythmia[59] in which abnormal thalamocortical theta activity leads to abnormal oscillations at beta/gamma bands, which eventually results in ongoing pain. Additionally, consistent with prior neuroimaging studies,[60] MEG studies in resting-state seems to show activation of default mode, salience, and central executive networks.

Potential for MEG to identify biomarkers of therapeutic improvement

Our search yielded only four interventional studies that used MEG to explore biomarkers of therapeutic improvement. This included two cohort studies[10,13] that used a visual paradigm on persons with migraine and two case studies that used a resting-state paradigm on a participant with FHM[23] and cluster headache.[31] Preventative

treatment with sodium valproate[10] and topiramate[13] in persons with migraine was found to exhibit differential MEG responses, including normalization of DC-MEG shifts and P100m response over the occipital cortex in response to flashing checkerboards. The longitudinal study on one participant with FHM showed lateralized alpha band desynchronization over the occipital lobe that resolved with pharmacological intervention. The study on cluster headache that used deep brain stimulation targeting the hypothalamus found MEG localized activity in the periaqueductal gray decreased while increasing the orbitofrontal cortex activity, post-therapy. Though preliminary, accumulated evidence shows MEG could potentially elucidate central mechanisms of action of both pharmaceutical and neuromodulation therapies. Interestingly, multiple studies also reported associations between changes in MEG metrics and clinical improvements, which could serve as motivation to investigate potential causal effects underlying these correlations. Recently, the US Food and Drug Administration has approved four monoclonal antibody treatments[61] directed toward the calcitonin gene–related peptide (CGRP), a molecule known to trigger migraine. MEG markers of anti-CGRP treatment[62] still seems to be an unexplored area.

Limitations

One of the main limitations in existing literature is that the findings from different studies are often not directly comparable due to high variability in the clinical characteristics of the population studied. Migraine is generally used as an umbrella term to describe many entities (e.g., with and without aura, chronic, episodic, acute, menstrual, hemiplegic, etc.), which further decompose into subcategories based on disease severity, occurrence of attacks, and so on. Problems with comparability are further exacerbated by inconsistent reporting standards (e.g., definition of interictal period, medication use relative to MEG scan, etc.). To facilitate reproducibility, inter-study comparability, and collection of homogeneous datasets, future research should consider the high dimensionality of the disease and follow proper reporting standards for MEG data.

Most of the studies found in our search results followed a case–control design that compared headache to a healthy control cohort. While all studies reported age and sex matching as a criterion for enrolling healthy controls, there was no evidence of the implementation of blinding procedures to avoid selection bias or bias related to data collection and analysis. In fact, several studies recruited healthy controls from employees at the hospital conducting the research or their friends and family, which could lead to systematic error in the association or outcomes.[63] Further, there was no evidence that studies involving lengthy repetitive stimulation paradigms (e.g., visually evoked P100m) controlled for fatigue or attentional factors, which tend to vary between patient population and healthy controls, likely influencing the results. Future studies should optimize selection procedures and implement better controls to enhance scientific rigor and validity of the findings.

The presence of different MEG metrics available (e.g., evoked responses, spectral power, varied connectivity metrics, graph-based metrics, etc.) and the low statistical power of group comparisons, are known to weaken evidence in MEG literature. Recent evidence[64] suggests that robust results require much higher sample sizes than the median of 22 to 24 participants noted here, which are often further parcellated into small subgroups according to group assignments or other factors. Though some of the findings (e.g., P100m in visual cortex) have been replicated, the idea of constructing a reliable mechanistic model of migraine based on MEG seems far-fetched at this point, given the amount of variability.

Another identified drawback is the paucity of ictal MEG studies because of the lack of portability. This means spontaneous attacks—that is, ictal periods—can only be recorded by chance, and headache episodes often needs to be triggered using agents while participants are in the MEG scanner. While EEG can offer a reliable alternative for ambulatory monitoring, its poor sensitivity to functional changes occurring during attacks is a concern.[65] However, with the advent of wearable MEG technology,[9] this limitation could be addressed in the future.

Unlike EEG, we recognize MEG is also expensive and inaccessible. This is one of the reasons for relatively few MEG studies originating from the same research groups, compared to EEG[65] or fMRI studies.[66] The need for larger sample sizes naturally posits the issue of increasing costs, time, and resources in generating reliable MEG studies in migraine. A potential solution to this problem could be found in data-sharing databases, such as OpenNeuro (https://openneuro.org/) or the OMEGA initiative (https://www.mcgill.ca/bic/neuroinformatics/omega). Another aspect that should be considered are data differences due to device characteristics, given MEG is a recent technology and constantly evolving. Because the current report included all studies since the inception of MEG, we note greater variability and differences arising due to device characteristics (e.g., variable number of sensors, gradiometers vs. magnetometers, etc.). Inter-scanner variability is an important factor complicating comparability of individual datasets but can be largely minimized when proper reporting standards are followed.[67] This could also facilitate big data approaches to data analysis, most notably applications involving machine learning.

Today, there is a lot of focus on machine learning approaches that can aid in the development of brain-based neurologic signatures for both pain[68] and migraine.[69] The success of these approaches lies in identifying the complex features that underlie high-dimensional data, through adequately powered human studies. Though preliminary studies[70,71] that looked at the reliability and generalizability of MEG-based electrophysiological features in migraine show promise, larger studies that can produce statistically meaningful effect sizes and higher statistical power are needed. Such studies could also inform precision medicine[72,73] to combine MEG-based features together with demographic, clinical, and genetic factors to help predict response to therapies.

Future directions

Migraine is increasingly being considered an oscillopathy—that is, an abnormality in neuronal brain activity—and MEG has the potential to uncover the underlying sources.[74] Oscillations can provide a mechanistic understanding of cortical excitability and dynamic information flow (learning and communication).[75] They could serve as objective inputs to clinical decision-making applications and targets for neuromodulation-based therapies. The earliest literature[7] that reported CSD in persons with migraine were MEG based; however recent advances in MEG technology provide greater potential for MEG to be utilized for advanced functional connectivity analysis.

Given the advancements in MEG technology, combining MEG with computational models is an upcoming technique and holds great promise to further our mechanistic understanding of brain dynamics in health and disease.[76] Going beyond local activity, MEG combined with computational models[77,78] (e.g., dynamic causal models) allows inference on latent states within a Bayesian framework based on brain activity. Given that migraine is not purely a sensory abnormality but involves a significant behavioral and/or psychological burden[52] (e.g., fear avoidance), computationally driven MEG techniques hold promise to correlate task-related changes in brain activity more directly to latent cognitive processes.

CONCLUSIONS

In this systematic review, we present the current state of MEG in migraine and primary headache disorders and findings to date. A relatively few MEG studies portray migraine and headache disorders primarily as a sensory deficit, while the affective dimension is largely unexplored. The affective dimension is often attributed to inadvertent exacerbation of pain, leading to disability. Further, comprehensive understanding of headache pathophysiology necessitates not merely asking the question of what symptoms and behaviors characterize the disease, but also answering questions of how symptoms and behaviors exacerbate disease to devise solutions. We accumulate evidence for the lack of computationally driven studies in MEG that can shed light on pathological mechanisms in migraine and primary headache disorders. Further, application of advanced data analysis including machine learning could isolate patterns of brain activity enabling discovery of functional biomarkers.[71]

AUTHOR CONTRIBUTIONS

Study concept and design: Raghavan Gopalakrishnan, Olivia Hogue, Neil Nero. *Acquisition of data*: Raghavan Gopalakrishnan, Neil Nero, Nitesh Singh Malan, Eric J. Dunn, Olivia Hogue. *Analysis and interpretation of data*: Nitesh Singh Malan, Eric J. Dunn, Nymisha Mandava, Raghavan Gopalakrishnan, Richard C. Burgess, MaryAnn Mays, Olivia Hogue. *Drafting of the manuscript*: Raghavan Gopalakrishnan, Nitesh Singh Malan, Nymisha Mandava, Eric J. Dunn, Richard C. Burgess, MaryAnn Mays, Olivia Hogue, Neil Nero. *Revising it for intellectual content*: Raghavan Gopalakrishnan, Olivia Hogue, Richard C. Burgess, MaryAnn Mays. *Final approval of the completed manuscript*: Raghavan Gopalakrishnan, Nitesh Singh Malan, Nymisha Mandava, Eric J. Dunn, Neil Nero, Richard C. Burgess, MaryAnn Mays, Olivia Hogue.

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CONFLICT OF INTEREST STATEMENT

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DATA AVAILABILITY STATEMENT

All included references in the present review article are available on the Internet. The full dataset, statistical code, and data collection form have been deposited in the Open Science Framework at https://osf.io/8wvsa/?view_only=3a5ce45ef822411a9f82141a9658f3dc.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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